Biomarkers in Langerhans cell histiocytosis-associated neurodegeneration A model for CNS Erdheim-Chester Disease?

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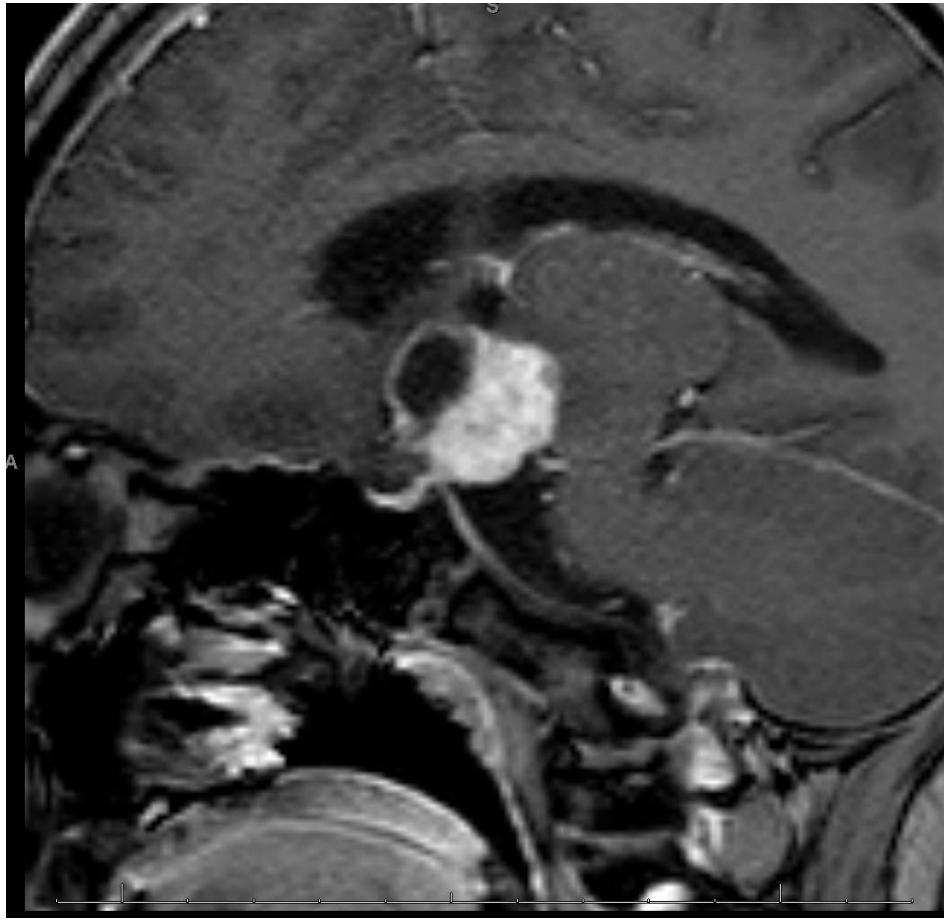
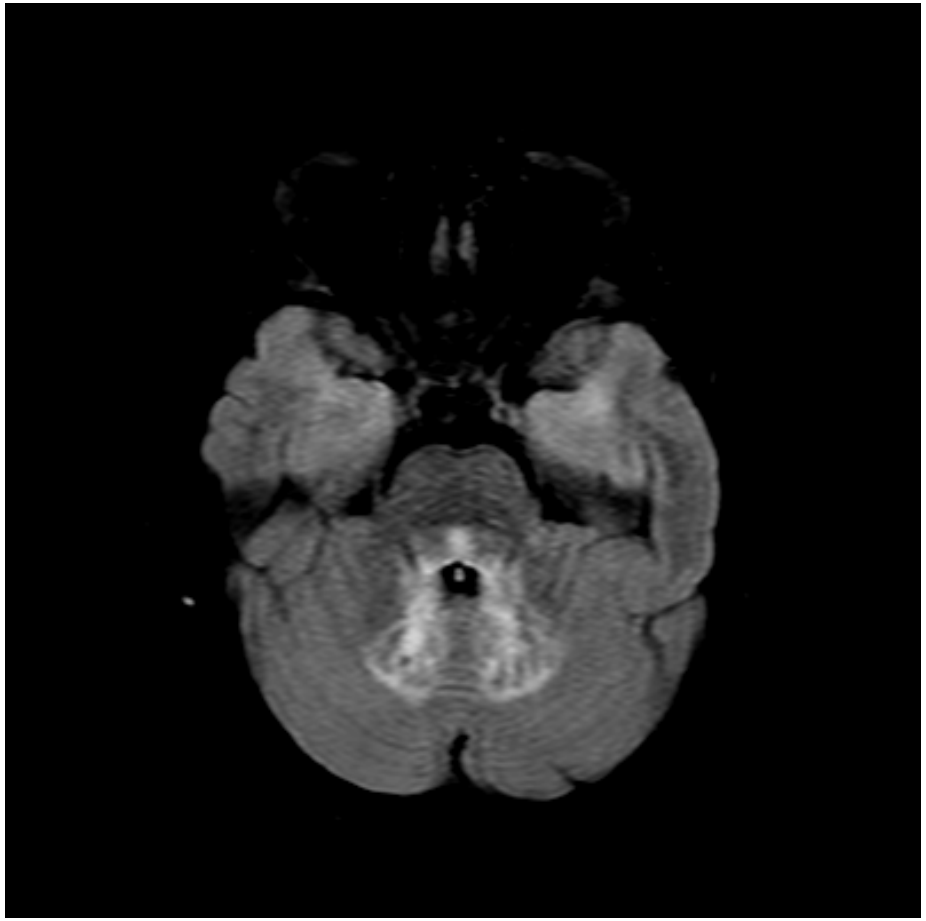
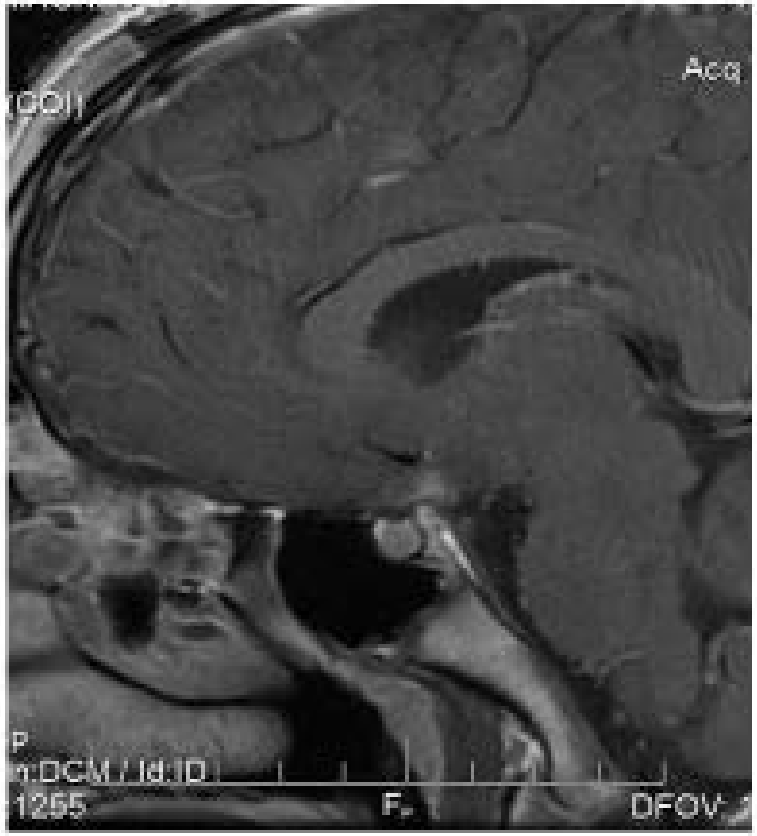
CNS LCH: Pituitary & Brain



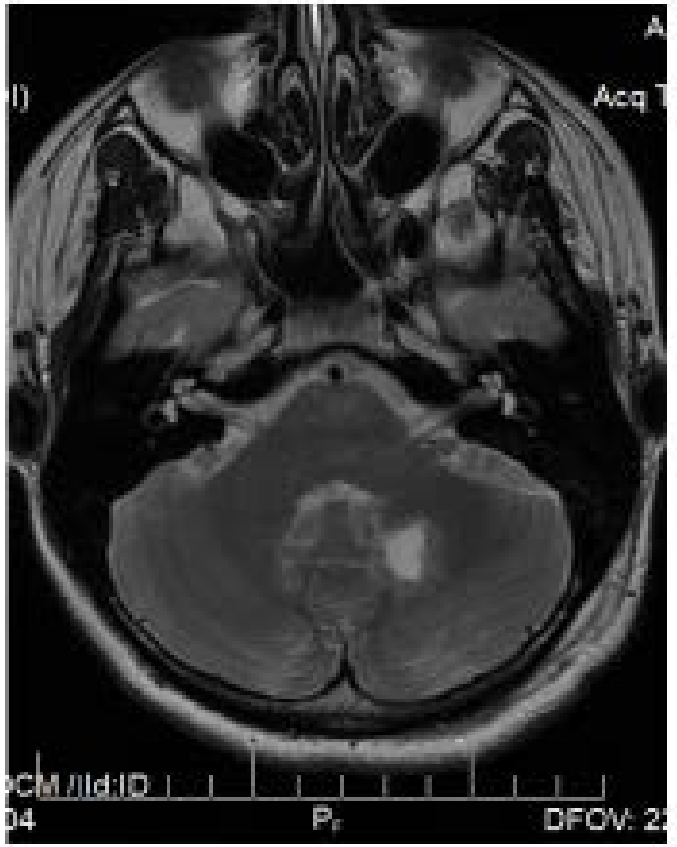


ECD Pituitary and Brain Involvement

T1 Post Contrast

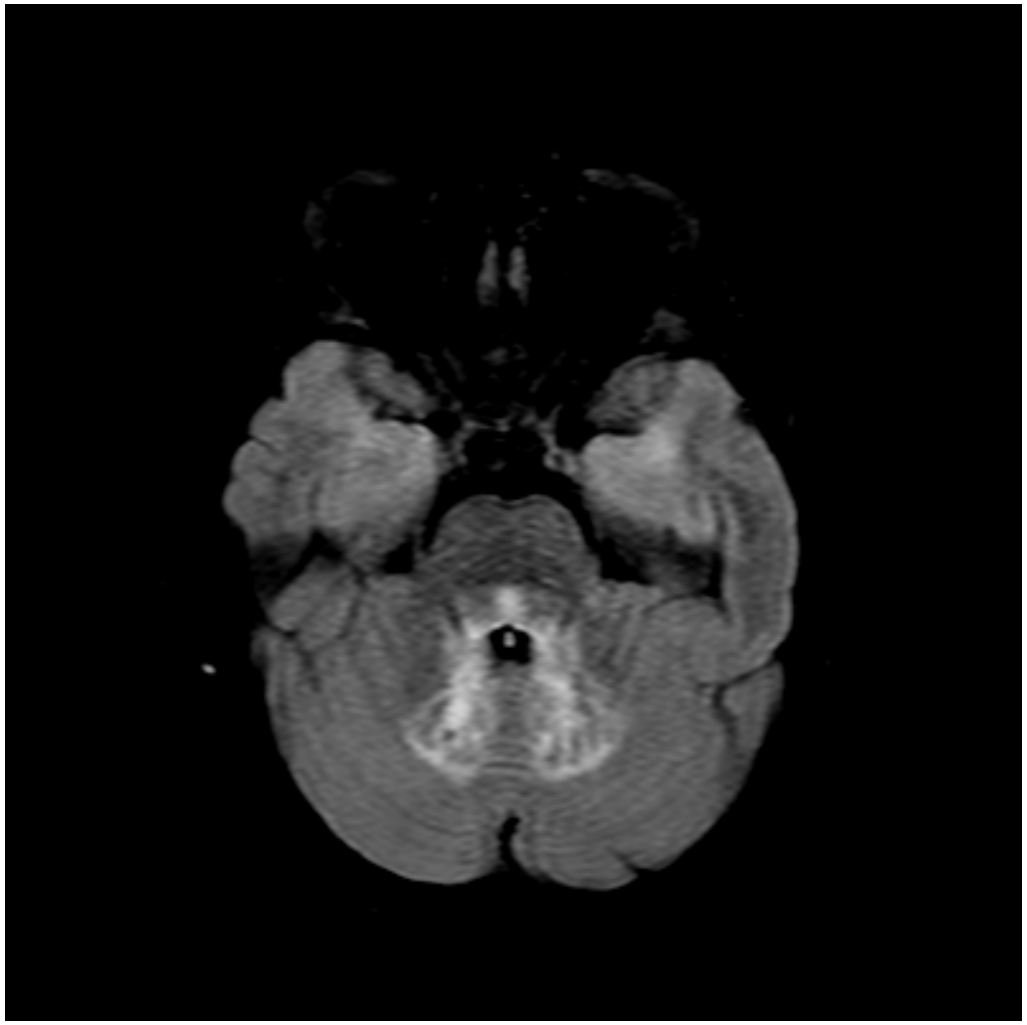


T2 FLAIR



LCH-ND

- 4-10% of all LCH patients
- Ataxia, dysarthria, dysmetria, behavioral changes or learning disabilities
- Months to years after presumed cure
- MRI: cerebellum, basal ganglia, pons, dentate nuclei
- Pathophysiology
  - Autoimmune?
  - Paraneoplastic ?
  - Other?

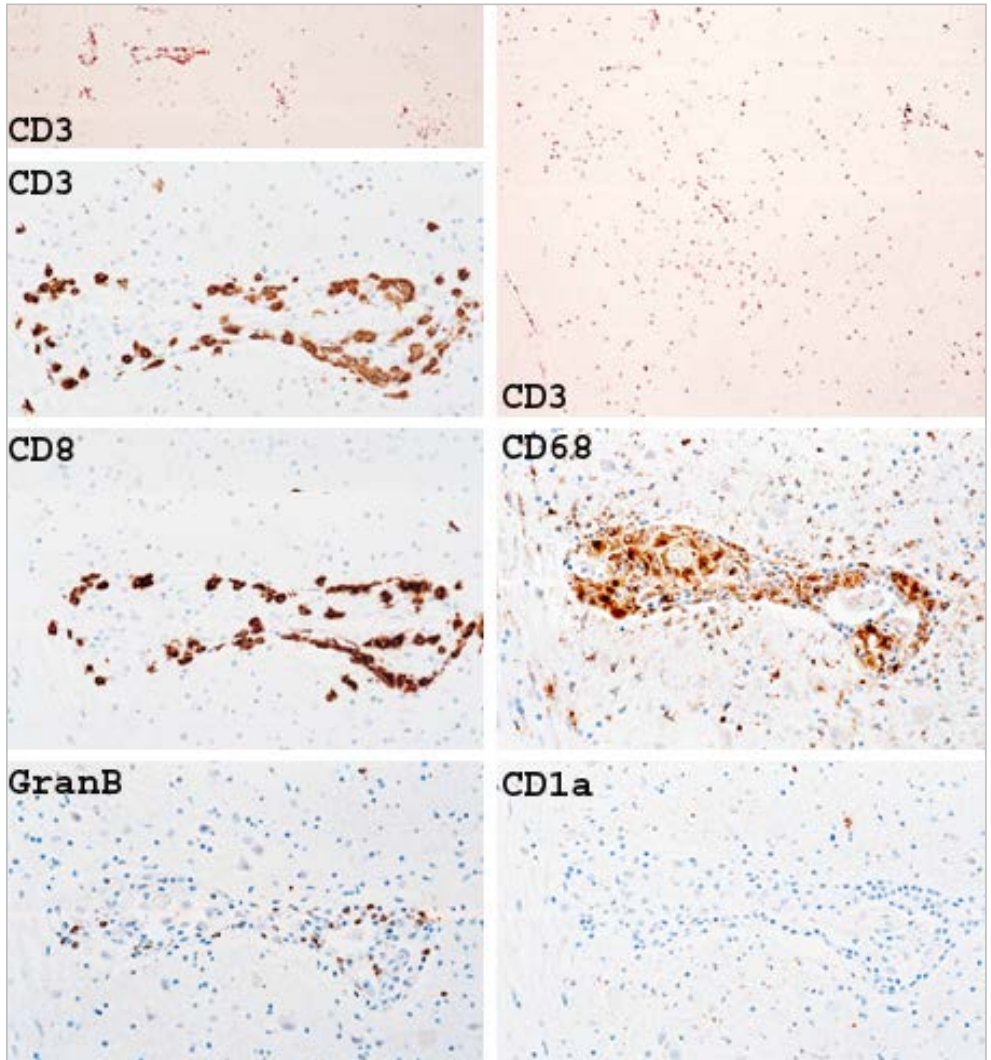


What is known about Etiology of ND-LCH?

- Not much
- Limited tissues to investigate: results published on 12 specimens
- Limited reagents used: CD1a, CD8, CD4, CD68
- No CD1a+ cells
- Prominent CD8+ infiltration
- Neuronal and axonal degeneration
- Secondary myelin loss
- Pathologic cells migrate from craniofacial bones/circumventricular organ to CSF, brain?

ND-LCH Cerebellum

N. Grois,, D. Prayer, H. Prosch & H. Lassman
Neuropathology of CNS Disease in LCH. *Brain* 2005



Hypotheses

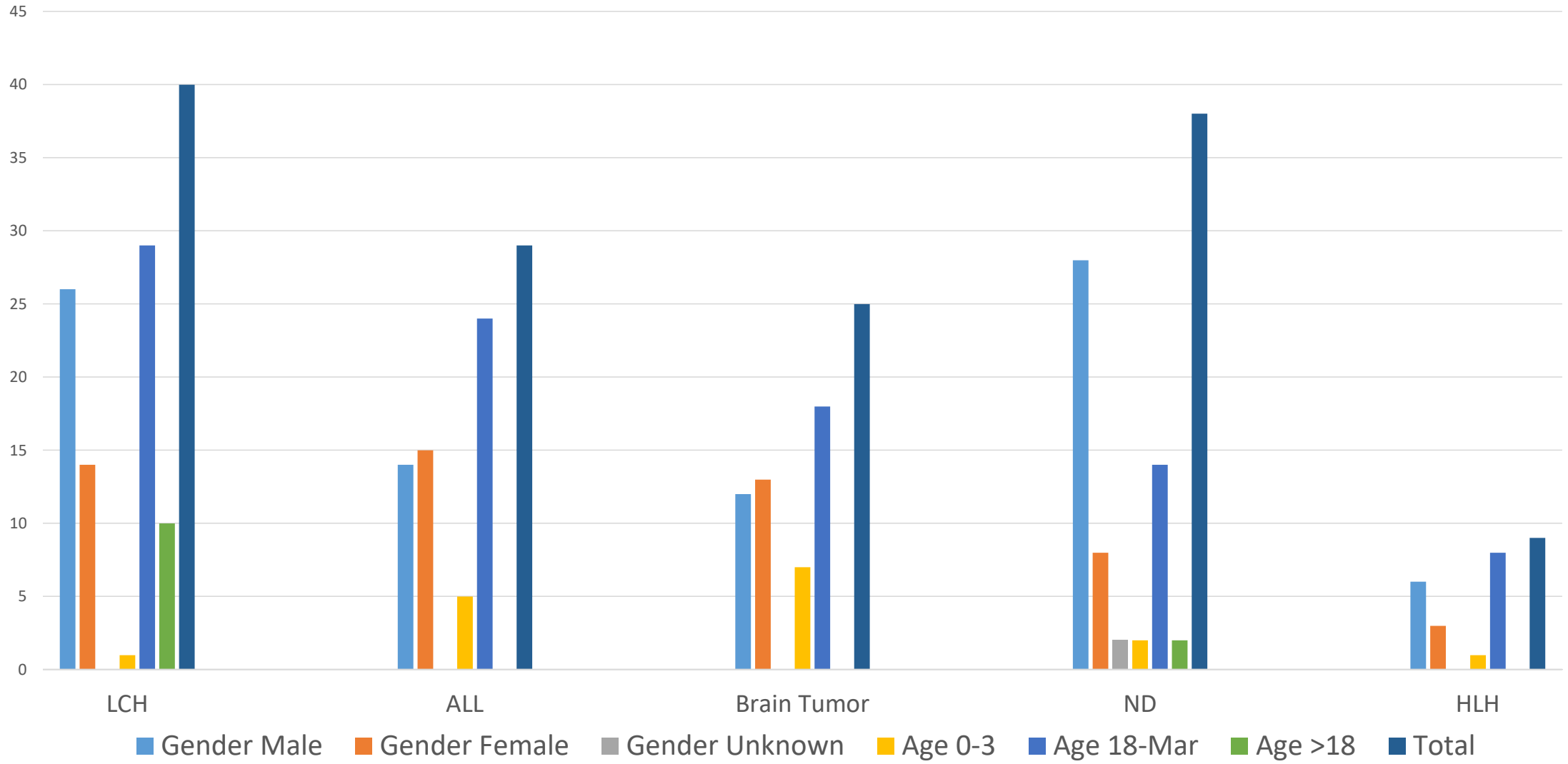
- Pathologic LCH cells and inflammatory cells secrete proteins creating unique CSF protein profiles
- Using BRAF V600E as a marker of pathologic LCH cells it may be possible to trace origin of and course of ND-LCH

Objectives

- Evaluation of biomarkers in patients with CNS manifestations of LCH
  - Define pathophysiology
  - Differentiate LCH from other CNS tumors
  - Develop Strategies Predict Development of LCH-ND

- Identify optimal treatment strategies

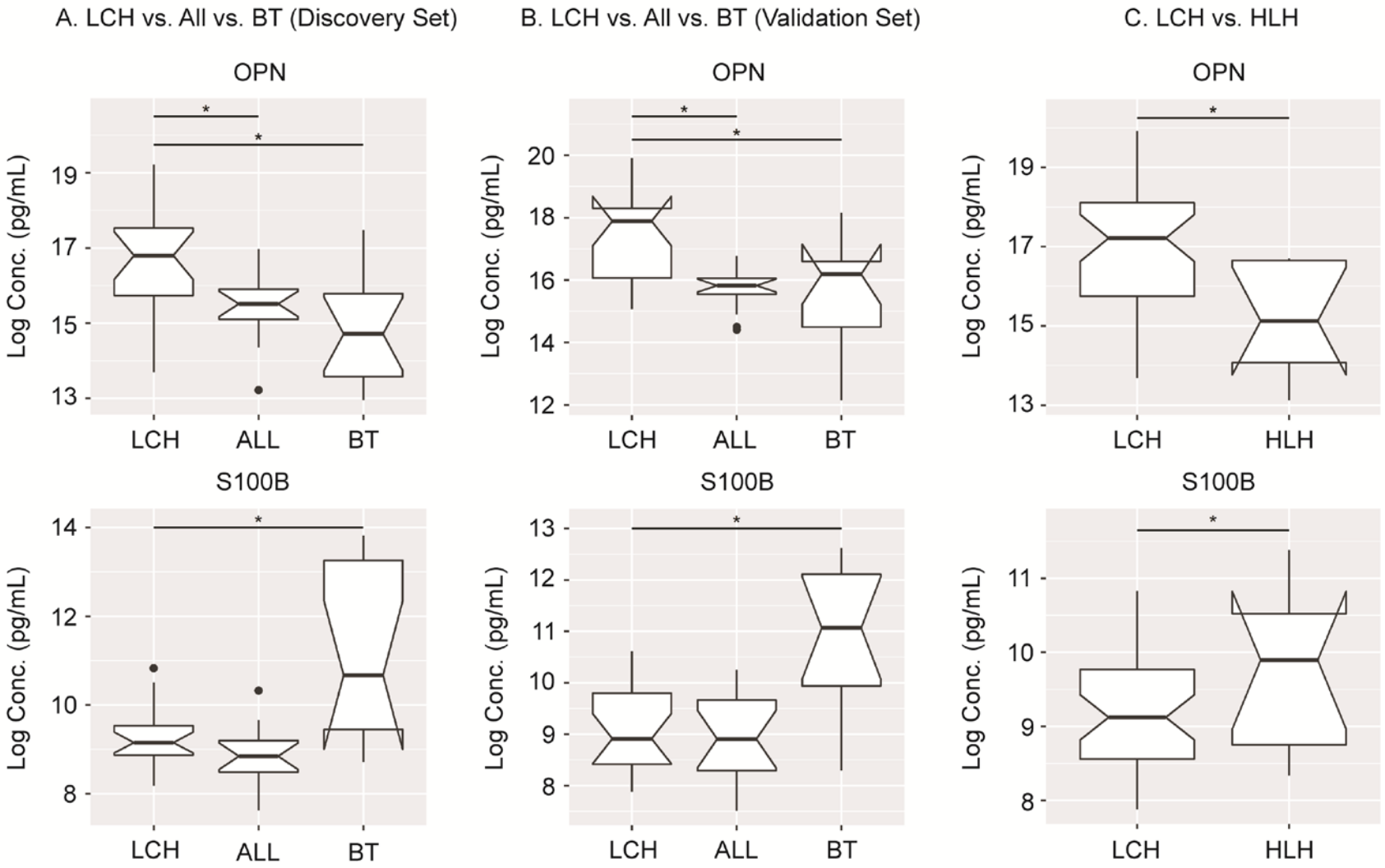
Patient Demographics n=40



Methods

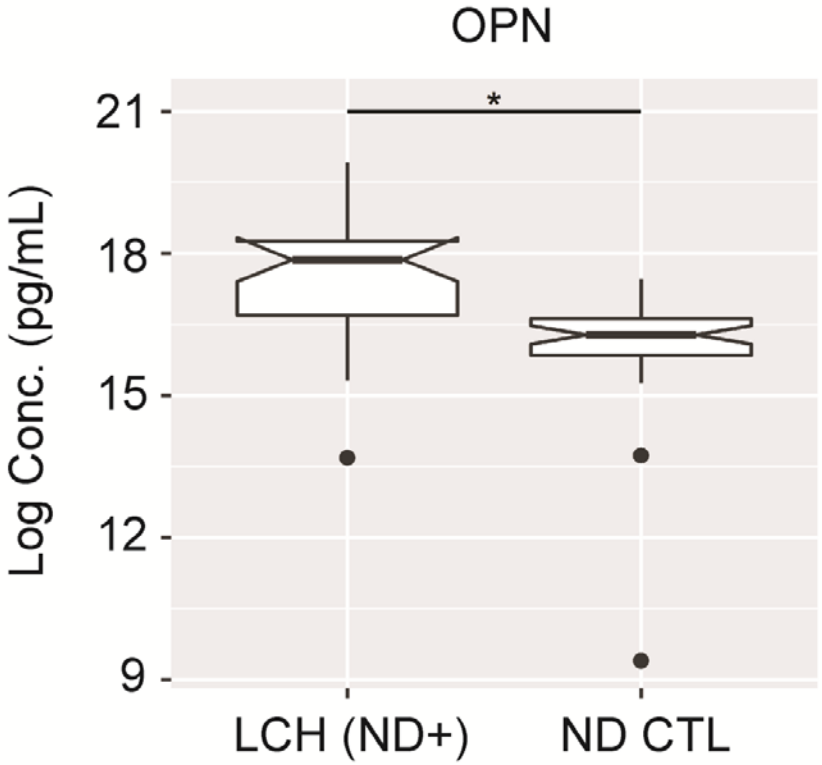
- Proteomics assay of CSF: 142 analytes using a Luminex platform Bio-informatic analysis to find best markers
- qPCR assay for *BRAF*V600E-mutated cells in CSF and blood
- Immuno-staining of brain sections for LCH cells, mutated BRAF protein, S100B, CD3
- qPCR of brain tissue for CD207 and Osteopontin

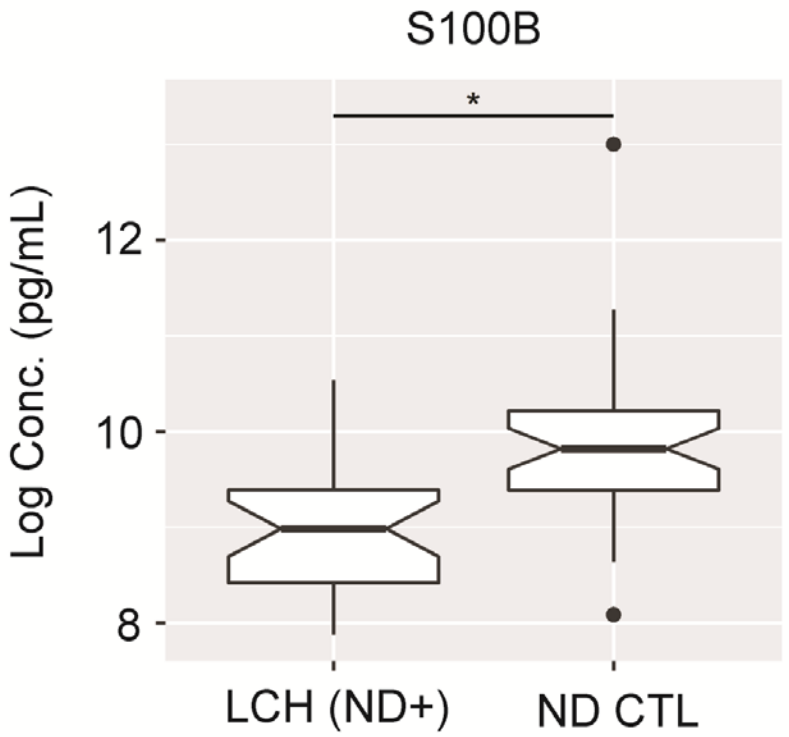
OPN and S100B in CSF



*P <0.05

Distinguishing LCH-ND vs ND controls

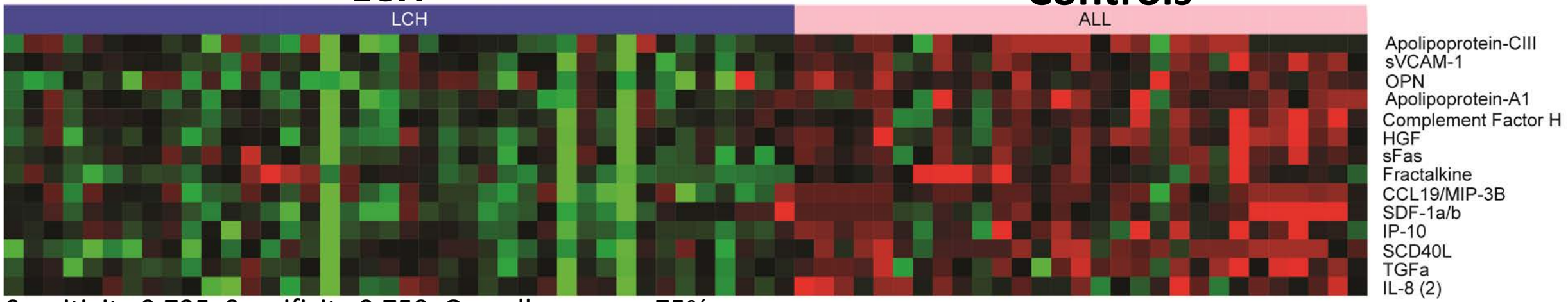




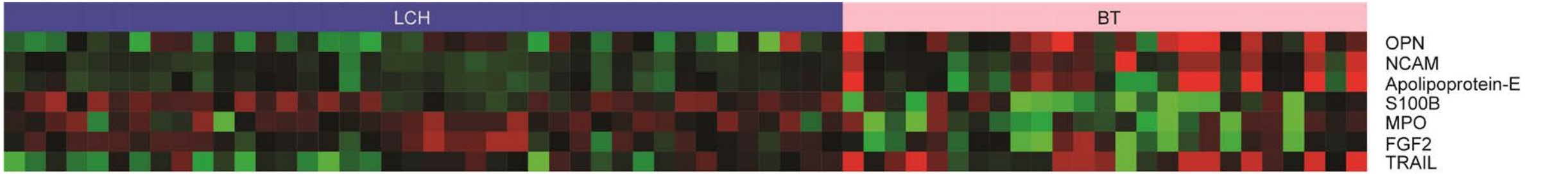
*P <0.05

Combinations of proteins differentiate ND-LCH from Controls

LCH **Controls**



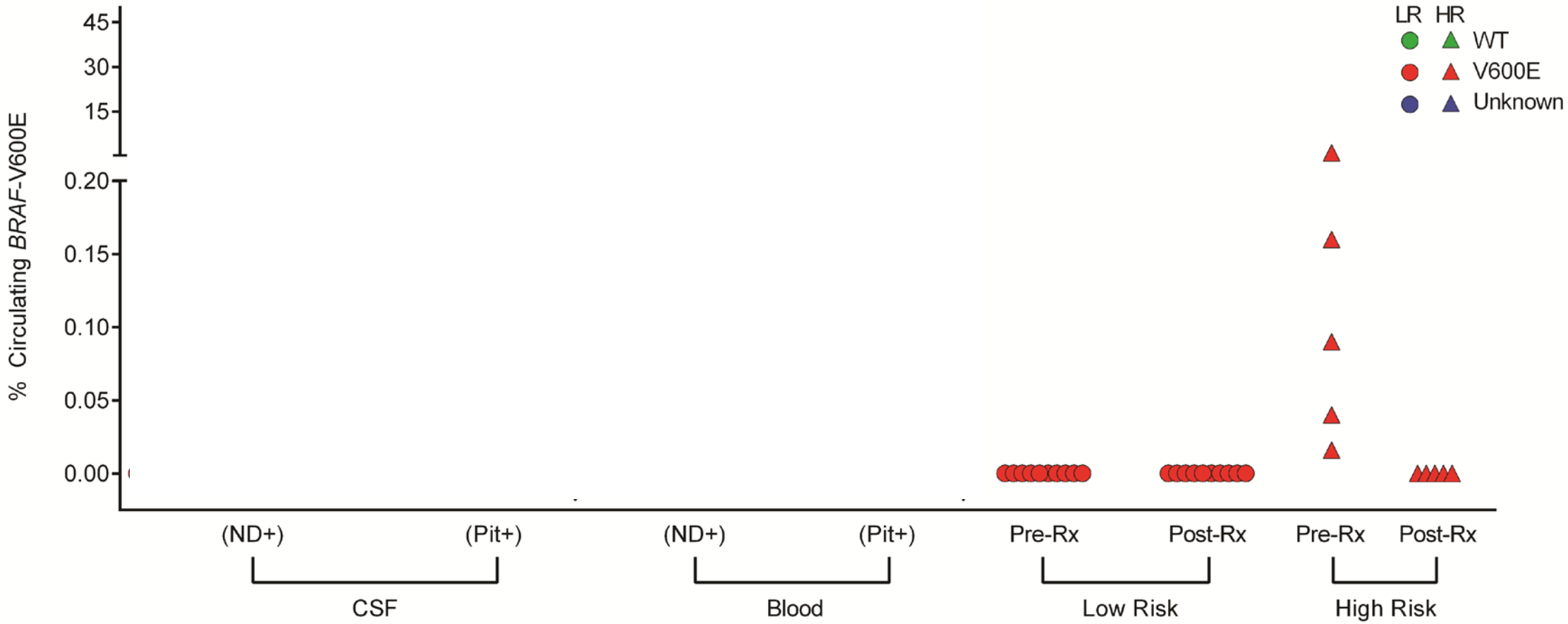
Sensitivity 0.725, Specificity 0.759, Overall accuracy 75%



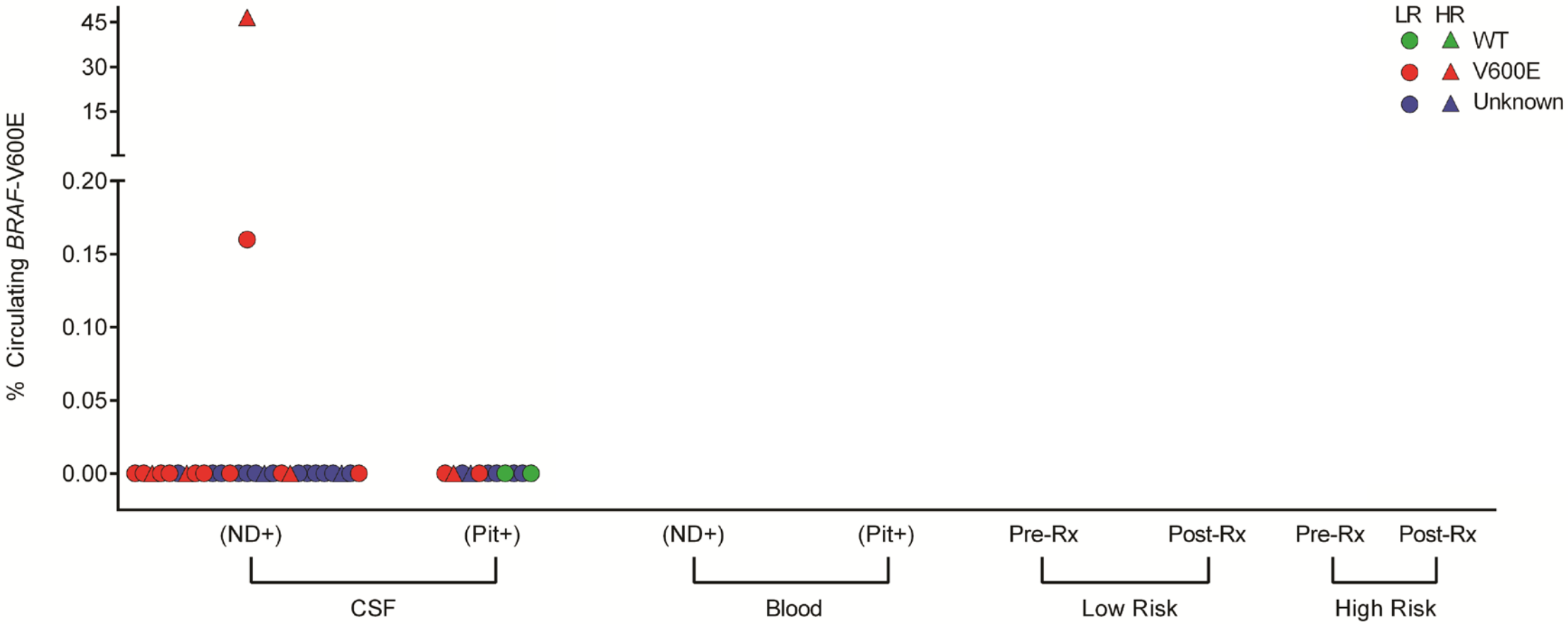
Sensitivity 0.975, Specificity 0.68, Overall accuracy 86%

Sensitivity 0.750, Specificity 0.763, Overall accuracy 76%

Circulating *BRAF-V600E* in LCH



BRAF-V600E cells in CSF of LCH-ND



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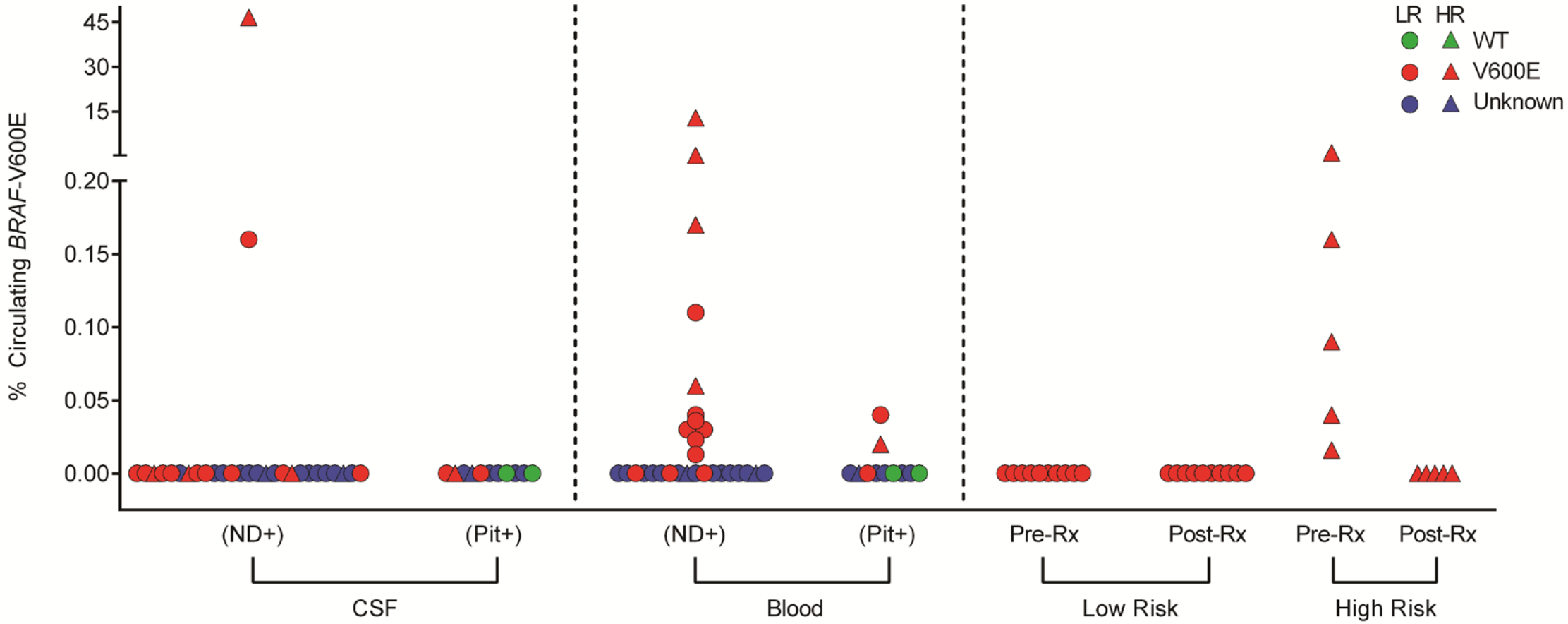
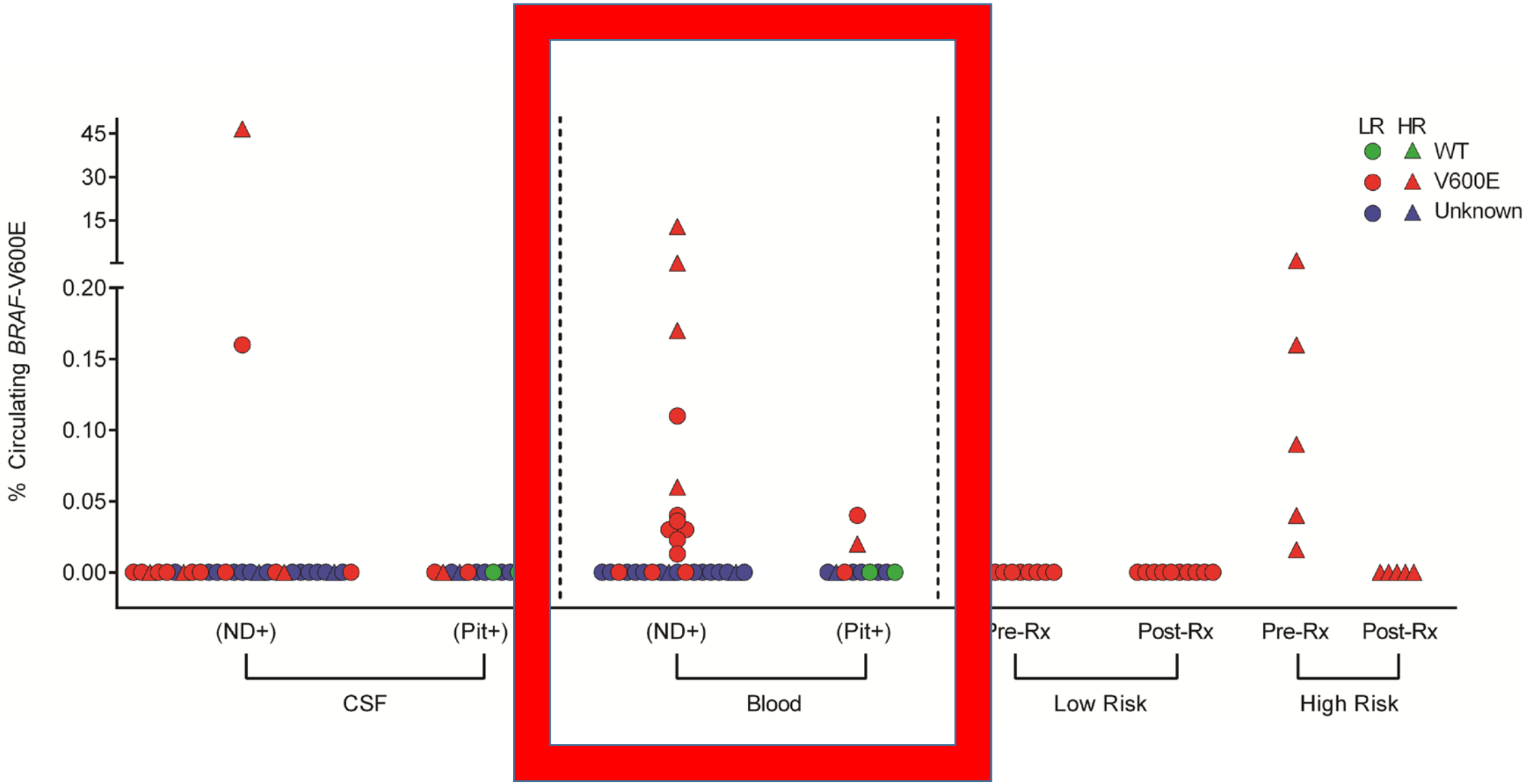
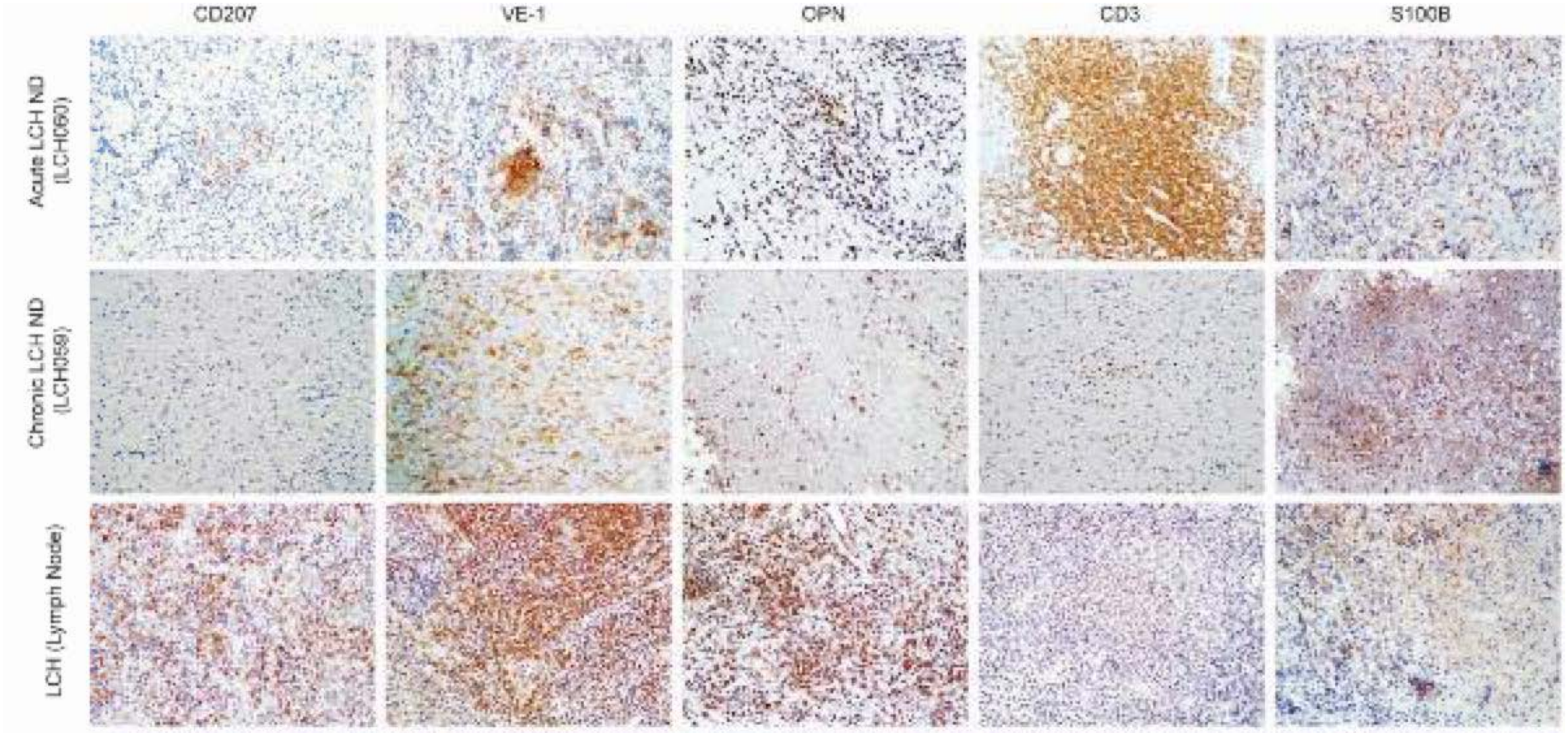


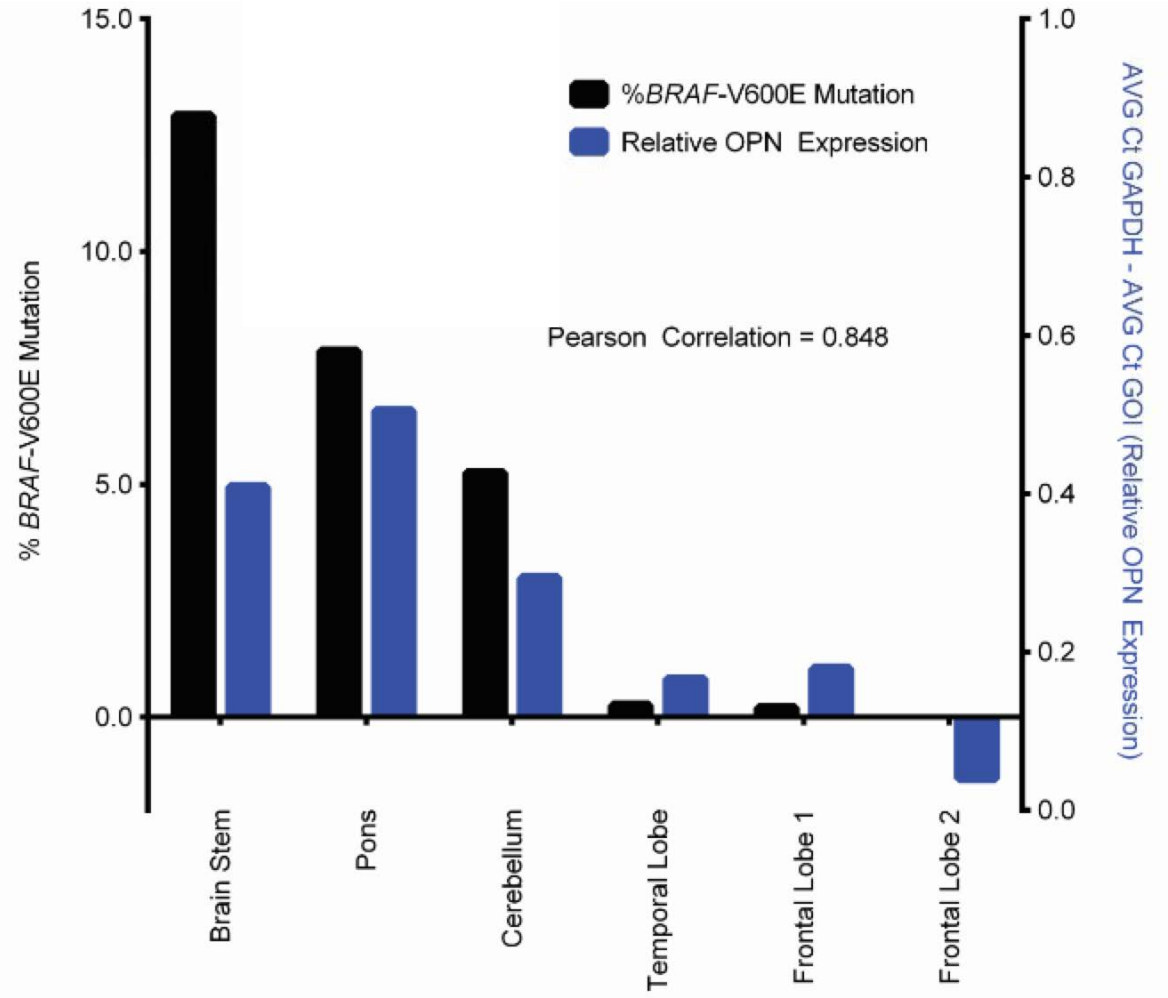
Circulating *BRAF-V600E* cells in LCH-ND

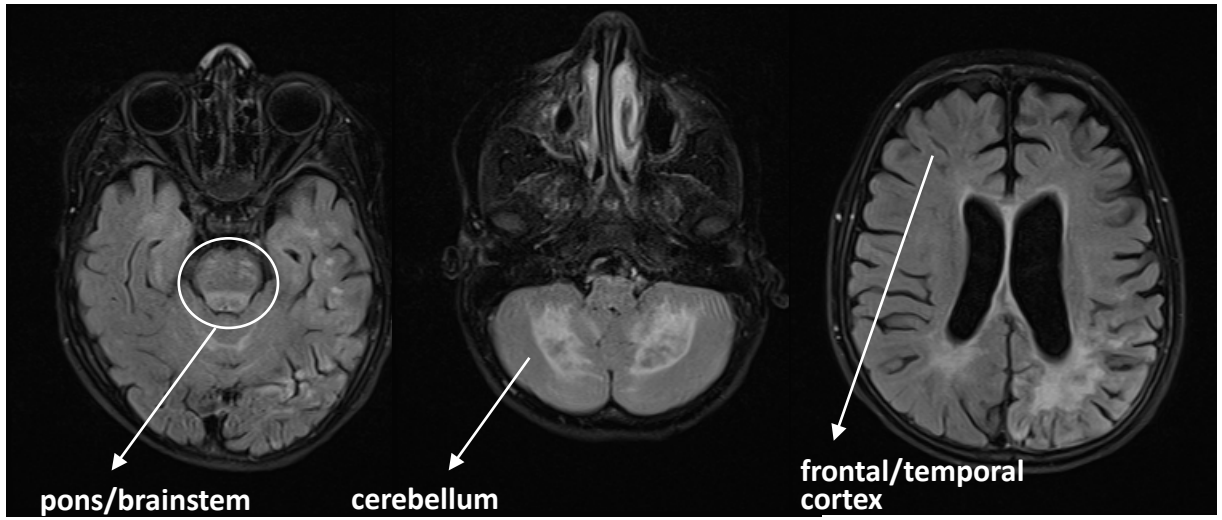


Immunohistochemistry

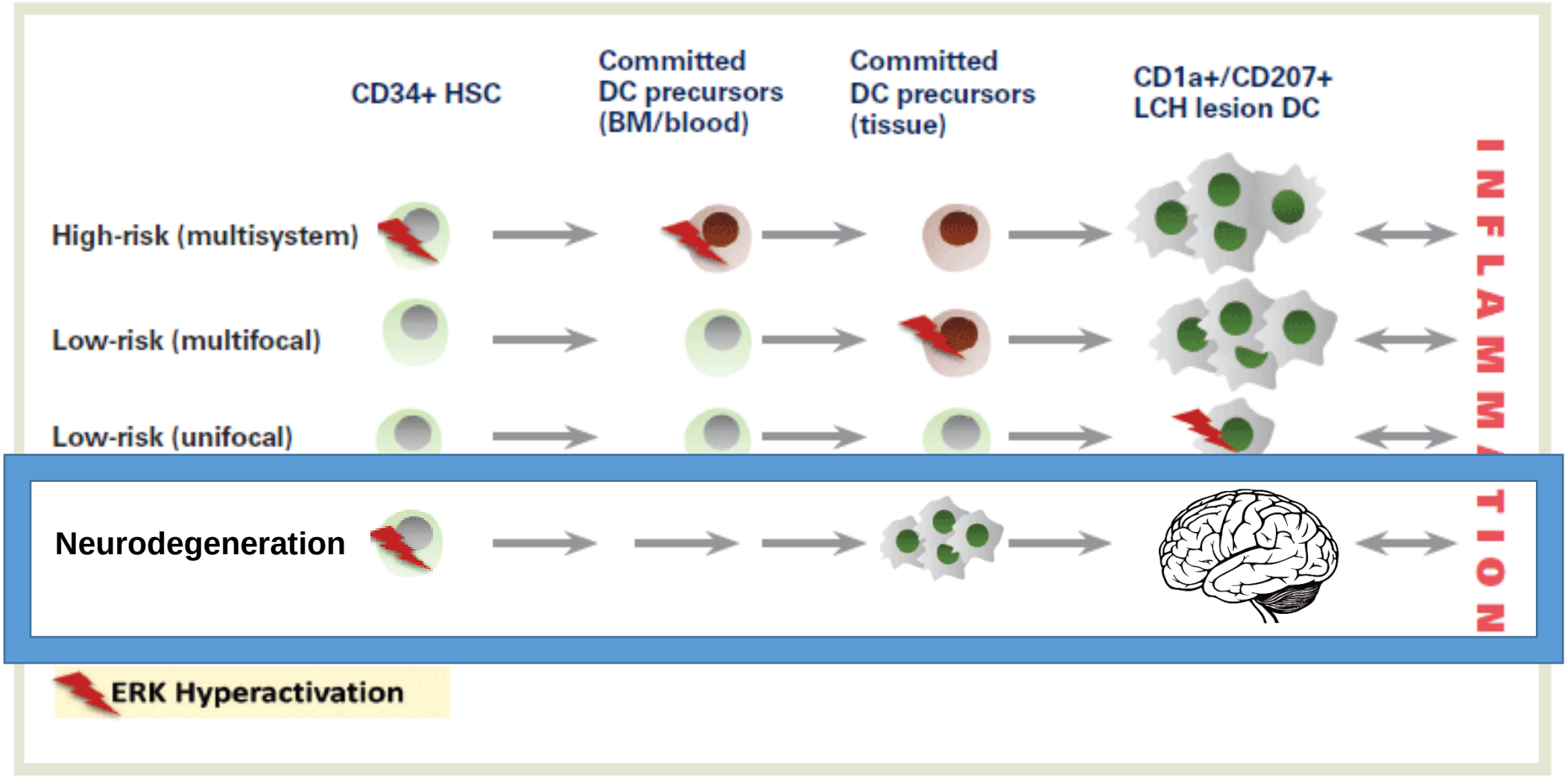


BRAF-V600E and OPN Expression by qPCR In Brain Tissue from Various Locations

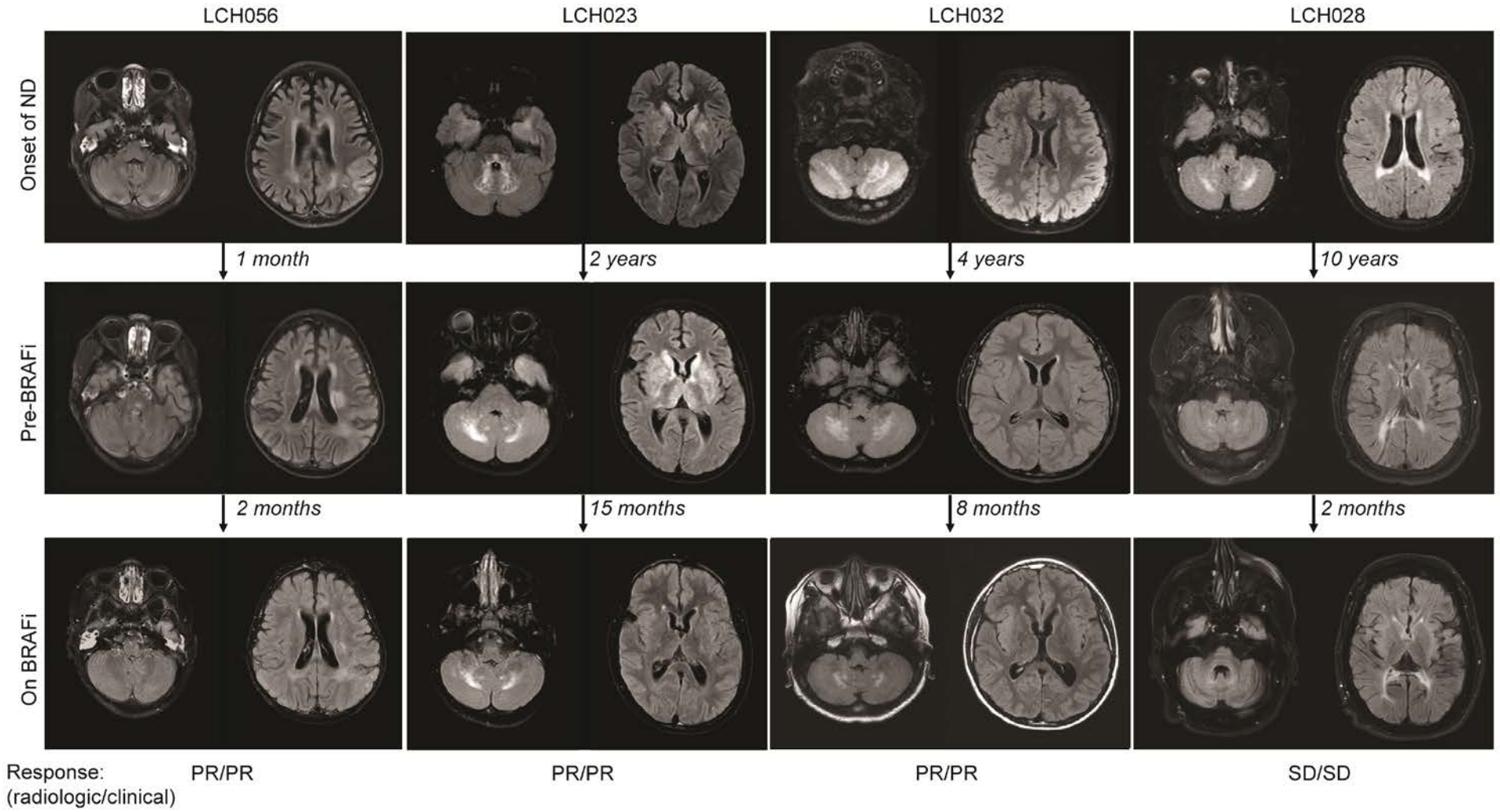




Proposed Model of LCH-ND



Clinical Response to Treatment with BRAF-inhibitors



Conclusions

- **Osteopontin is a reliable marker of LCH CNS Involvement**
- **Identification of circulating and "brain-resident" *BRAF*-V600E mutated cells suggests they play a major role in neurodegeneration**
- **Targeted therapy for *BRAF* or other *MAP* kinase genes is likely the best option for LCH patients with neurodegeneration**
- **Investigation of ECD patients with CNS involvement is warrented**

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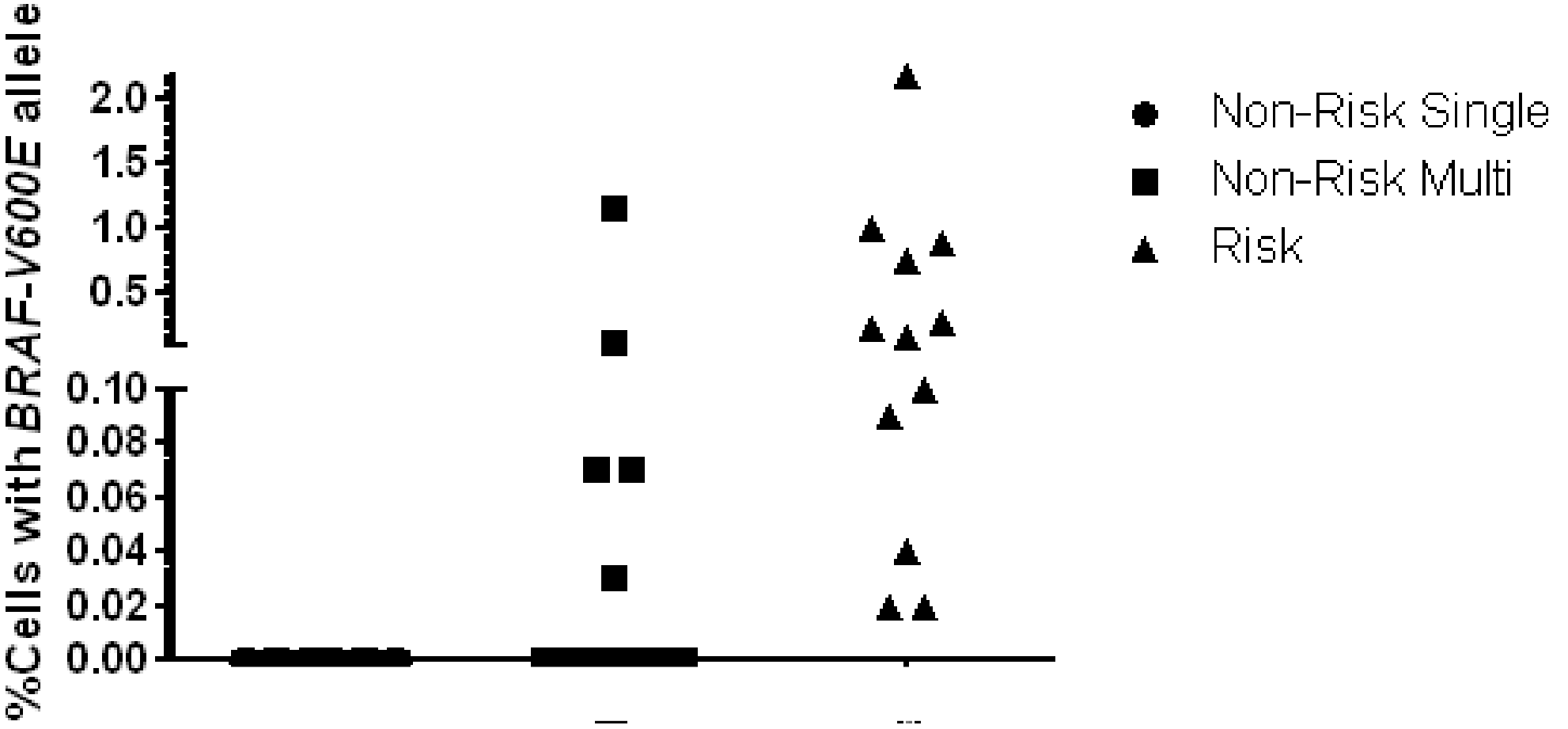
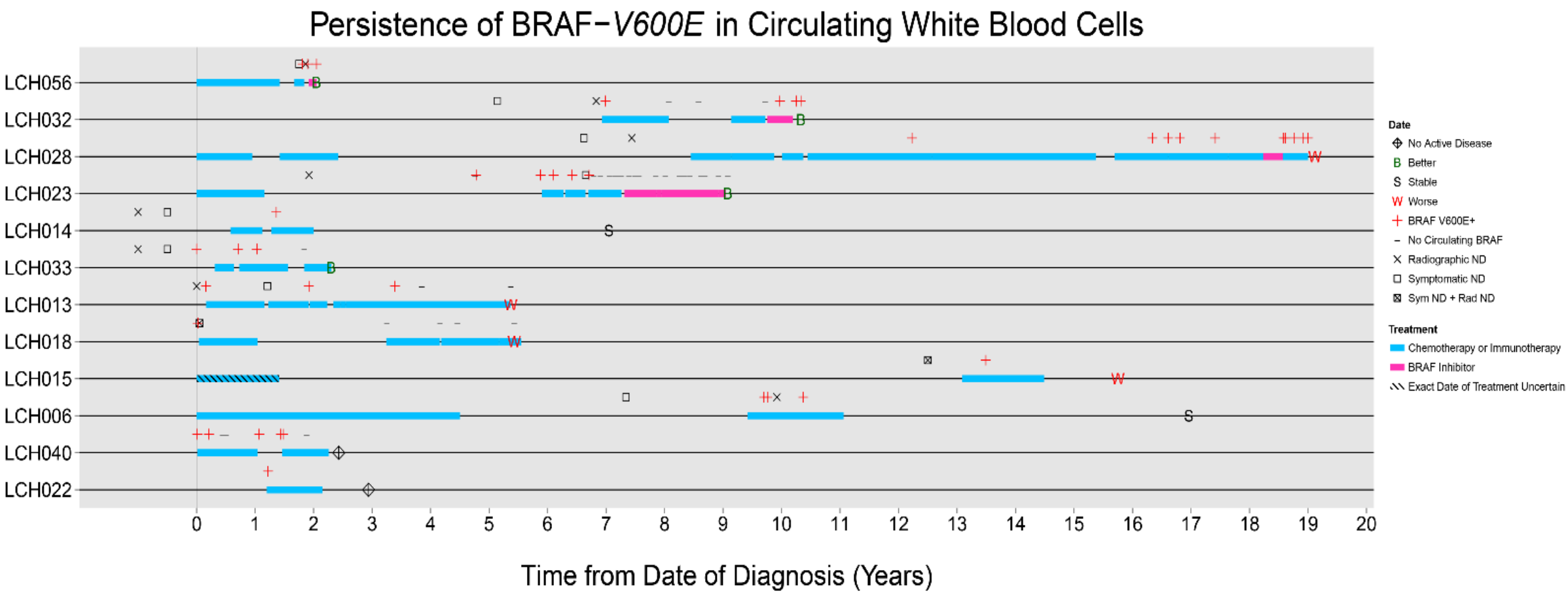
Circulating WBCs Harbor *BRAF-V600E* Mutation in High Risk LCH



Berres et al., *JEM* 2015

		LCH	ALL	Brain Tumor	ND	HLH
Gender	Male	26	14	12	28	6
	Female	14	15	13	8	3
	Unknown	-	-	-	2	-
Age	0-3	1	5	7	2	1
	3-18	29	24	18	14	8
	>18	10	-	-	2	-
Subtype		ND: 10 ND + Pit: 18 Pit: 12	Induction: 2 Consolidation: 1 Maintenance: 15 Other: 11	Medulloblastoma: 13 Meningeal Sarcoma: 1 Ependymoma: 3 Astrocytoma: 2 Germinoma: 2 Craniopharyngioma: 1 ATRT: 2 Pineal Mass: 1	X-LALD: 10 Alzheimer's: 15 Multiple Sclerosis: 3 Parkinson's: 6 Batten Dx: 2 Multi-organ Failure: 1 Other: 1	-
Total		40	29	25	38	9

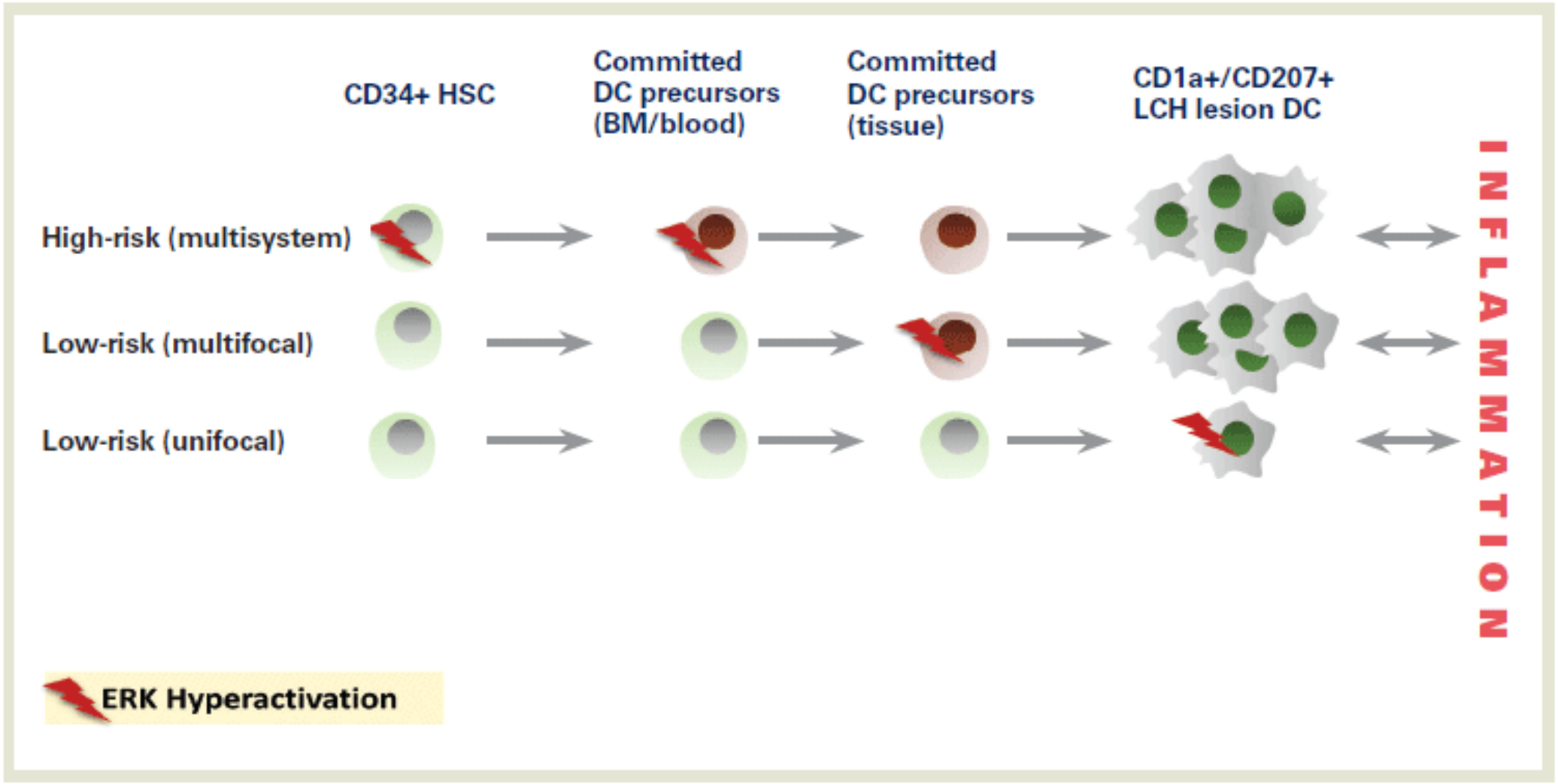
Clinical Courses



Multiple Sub-fractions Harbor BRAF-*V600E*

MB Number	BRAF % Unsorted	T-Cells CD3	B-Cells CD19	Macs CD64	Mono/KN CD16	DC Precursor CD11c	Meyloid DC CD11c + CD14	Neg Fraction CD11c- CD14-
LCH028	0.08	Yes						
LCH023	0.04						Yes	
LCH014	0.17				Yes	Yes		
LCH006	0.03	Yes						
LCH013	<0.02	Yes		Yes	Yes		Yes	
LCH015	<0.02							
LCH022	0.04				Yes			
LCH040	0.02		Yes	Yes		Yes	Yes	Yes

Misguided Myeloid Dendritic Cell Model



Zinn et al. *Oncology*. 2016